REMARKS

I. Status of Claims:

Upon entry of the instant amendment, claims 1-10, 17-24, and 29-46 will be pending, claims 11-16 and 25-28 having been canceled without prejudice and new claims 29-46 added. Support for the amended and new claims can be found, for example, at page 14, lines 25-30; page 18, lines 15-28; page 19, line 20 to page 20, line 4. Applicants reserve the right to pursue the subject matter of the canceled claims in this or a future related application.

Claims 1-10 and 22-24 are under examination. Applicants believe that new claims 32-34, and possibly new claims 35-46, belong in the presently elected group. Applicants note that upon allowance of the product claims (*i.e.,* claims 1-10, 22-24, and 32-34), the process claims (*i.e.,* claim 21 and new claims 29-31 and 35-36) will be rejoined (*see,* Restriction Requirement, section 5, pages 4-5).

The Office Action Summary indicated that claims 8-15 are objected to (*see,* "Disposition of Claims, section 7). In addition, the Action stated that:

> Claims 8-15 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claim" (*see,* Office Action, page 17, section 15).

Applicants submit that claims 8-15 are independent claims and thus do not depend on any rejected base claim. Accordingly, claims 8-15 should have been indicated as allowable in the Action, since no rejections have been directed against those claims. Applicants respectfully request that the next Office Communication clarify this matter.

II. Information Disclosure Statement:

Applicants thank the Examiner for reviewing the information disclosure statements (IDS) submitted on May 21, 2007, October 4, 2007, February 12, 2008, June 11, 2008, September 13, 2008, January 20, 2009, February 9, 2009, February 24, 2009, and March 27, 2009 (*see,* Office Action, page 3, section 4).

The Action says that the listing of references in the specification is not a proper IDS, and therefore, unless the references are submitted in a separate paper or cited by the examiner on

form PTO-892, they have not been considered. Applicants point out that the references listed on page 2, lines 11-17, were submitted on a PTO Form-1449 on May 21, 2007 (*see,* Desig ID A56, A58, A59, A60, A65, A79, and A99) and were considered by the Examiner on February 20, 2009.

Applicants respectfully request that the Examiner consider the references cited in the PTO Form-1449 accompanying this Amendment and return an initialed copy of the Form-1449 with the next Official Communication.

III. Objections to the Specification:

The Action objected to the disclosure because the specification contained sequences on pages 8 and 20 that were not identified by a SEQ ID NO and were not included in the Sequence Listing (*see,* Office Action, page 3, section 6).

The specification has been amended to incorporate SEQ ID NOs for sequences that were not previously so-identified. In addition, a new Sequence Listing that includes these sequences is submitted with this Amendment. Accordingly, Applicants respectfully submit that the grounds for this objection are moot.

IV. Title:

The Action stated that the title of the invention is not descriptive (*see,* Office Action, page 4, section 7).

The title has been replaced with the following new title: "Single Chain Polypeptide Antibodies that Bind Human Leukocyte Antigen." In view of this amendment, Applicants submit that the ground for this objection is moot.

V. Rejections Under 35 U.S.C. § 112, First Paragraph:

Claim 16 stands rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with both the written description and enablement rejections (*see,* Office Action, pages 4-13, sections 9 and 10).

Claim 16 has been canceled without prejudice in the present amendment. Accordingly these rejections are moot.

VI. Rejection Under 35 U.S.C. § 103:

Claims 1-7 and 22-28 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Ozaki *et al.* (*Blood*, **102**:933a (2003)) in view of Kortt *et al.* (*Biomol. Engg.*, **8**:97-108 (2001)) (*see,* Office Action, pages 14-17, section 14)[1]. Claims 25-28 are canceled, so this rejection is moot as to them.

With respect to Ozaki, the Action states that:

> Ozaki et al. teach a recombinant scfv diabody which binds to HLA and has a cell death inducing function, a cell growth inhibitory function, and an anti myeloma (blood tumor) function. Ozaki, et al. do not teach an sc(Fv)2 antibody. This deficiency is made up for in the teachings of Kortt , et al. (*see,* Office Action, page 15, last paragraph).

With respect to Kortt, the Action states that:

> Kortt, et al. teach how the length of the linker affects the formation of scfv multimers including sc(Fv)2 (see pages 96 1st column and figure 3). Kortt, et al. teach linkers for scFv molecules to be up to 15 amino acids long (figure 3). (*see,* Office Action, page 16, first paragraph).

In support of combining Ozaki with Kortt, the Action alleges:

> One of ordinary skill would have been motivated to and had a reasonable expectation of success to have used the antibody of Ozaki, et al. to produce an sc(Fv)2 which maintained the cell death inducing, cell growth inhibiting and anti myeloma functions in view of Kortt, et al. because Kortt et al. teach that scFv multimers (i.e. sc(Fv)2) are significantly larger than scFv monomers and thus have an advantage in *in vivo* application by minimizing the rapid first pass clearance rate of the molecule (page 103, 5. Size of di- and tri-abodies and effect on *in vivo* pharmacokinetics). Kortt, et al. also teach the advantage of multivalent scFvs over monovalent scfvs is the gain in functional binding affinity to target antigens. (page 104, 6. Avidity and flexibility in scfv multimers). (*see,* Office Action, page 16, third paragraph).

Applicants respectfully traverse this rejection. To establish a *prima facie* case of obviousness, the Office must:

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[1] The Action states that the "[b]ased upon the earlier effective filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e)" (*see,* Office Action, page 14, second full paragraph, second sentence). As both cited references are neither patents nor patent application publications, both references can not constitute art under 35 U.S.C. § 102(e). Applicants have assumed that the Action intended to say that the cited art constitutes prior art under 35 U.S.C. § 102(a).

(i) identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does;

(ii) establish that there was a reasonable expectation of success in the art; and

(iii) show that all claim limitations are taught or suggested by the combination of cited references. *See,* MPEP § 2143 and *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417-18 (2007). In combining references to support an obviousness rejection, the Office must consider a prior art reference in its entirety, *i.e.,* as a whole, including portions that would lead away from the claimed invention. *See, W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). When the prior art teaches away from combining certain known elements, an invention that combines those elements is likely to be non-obvious. *KSR Int'l Co.*, 550 U.S. at 416.

In the present case, there are at least two reasons supporting the non-obviousness of the claimed invention. First, combining the cited references does not result in the claimed invention. Second, the Kortt reference teaches away from the claimed invention.

Before delving into the arguments, Applicants would like to clarify some of the relevant terms that are relevant to this rejection:

An **scFv monomer** is a single chain polypeptide that consists of one heavy chain variable region and one light chain variable region, usually with a peptide linker between them.

An **sc(Fv)2** is a single chain polypeptide that consists of two heavy chain variable regions and two light chain variable regions, usually with a polypeptide linker separating each variable region from the next.

An ***scFv diabody*** is a dimer formed by the non-covalent interaction of two scFv monomers. To be clear, an scFv diabody is **not** a single chain polypeptide, but rather contains two chains that associate non-covalently.

The sole independent claim under examination, claim 1, recites: An antibody comprising two heavy chain variable regions and two light chain variable regions, wherein the antibody is a **single chain polypeptide** having a binding activity against human leukocyte antigen (HLA). (emphasis supplied).

Ozaki *et al.* teach a monoclonal antibody (2D7) as well as **a single-chain Fv diabody (2D7-DB)**. Ozaki teaches that, while 2D7 induced cytotoxicity only in the presence of secondary goat anti-mouse IgG, 2D7-DB effectively cross-linked HLA-A and induced cell death by itself. In addition, 2D7-DB was found to have *in vivo* efficacy in SCID mice inoculated intravenously with myeloma cell line ARH-77.

Kortt *et al.* describe the design and expression of diabodies (dimers), triabodies (trimers) and tetrabodies (tetramers) (*see,* title and abstract). This reference states:

> This review describes how the length of the linker joining the V-domains and selection of the V-domain orientation can be used to create new **non-covalent oligomeric forms** of Fv modules of different size, flexibility and increased valency suited for in vivo imaging and therapy. (*see,* page 96, left column, first full paragraph, second sentence). (emphasis supplied).

In other words, Kortt is not directed to *single chain* sc(Fv)2 molecules as asserted by the Action (*see,* page 16, first and third paragraphs), but rather to non-covalent oligomers containing multiple chains (*e.g.,* diabodies containing two chains, triabodies containing three chains and tetrabodies containing four chains).

Even if there were some reason to modify Ozaki with Kortt (which Applicants do not concede), the combination of Ozaki and Kortt would not teach all claim limitations, because neither reference teaches or suggests one should modify diabodies into sc(Fv)2 polypeptides. Instead of teaching the use of sc(Fv)2 molecules, Kortt is entirely directed at emphasizing the benefits of multi-chain, oligomeric forms of Fv modules, such as diabodies.

Moreover, Kortt actually **teaches away** from modifying the 2D7-DB of Ozaki into an sc(Fv)2 molecule.

With respect to teaching away, the Supreme Court in *KSR Int'l*, 550 U.S. at 416, stated in relevant part:

> In *United States v. Adams*, 383 U.S. 39, 40 (1966), a companion case to *Graham*, the Court considered the obviousness of a "wet battery" that varied from prior designs in two ways: It contained water, rather than the acids conventionally employed in storage batteries; and its electrodes were magnesium and cuprous chloride, rather than zinc and silver chloride. The Court recognized that when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result. 383 U.S. at 50-51. It nevertheless rejected the Government's claim that Adams's battery was obvious. The Court relied upon the corollary principle that *when the prior art teaches*

away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious. Id. at 51-52. *When Adams designed his battery, the prior art warned that risks were involved in using the types of electrodes he employed. The fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that Adams's design was not obvious to those skilled in the art.* (emphasis supplied).

In the context of the present application, Kortt states:

> Although several groups continue to develop covalent scFv dimers [*i.e.*, sc(Fv)2], we predict that diabodies will be more stable than these scFv dimers. Indeed, the linkers in diabodies and tetrabodies are apparently relatively inaccessible to protease compared with the long linkers required to join two monomeric scFv. (*see,* page 104, left column, first paragraph) (emphasis supplied).
> . . .
> Pre-clinical biodistribution studies have shown that diabodies offer significant advantages over (scFv)2 and F(ab)2 for imaging and therapy and will no doubt be in clinical trials within 12-24 months. (*see,* page 106, Conclusions) (emphasis supplied).
> . . .
> By providing a highly stable, protease-resistant scaffold, recombinant scFv multimers will become the paradigm for high-affinity protein-based therapeutic and diagnostic reagents. (*see,* page 106, Conclusions) (emphasis supplied).

In striking contrast to Kortt's teaching-away from the use of sc(Fv)2 as being less stable than diabodies, Applicants have surprisingly shown that the opposite is true: the presently claimed sc(Fv)2 is more stable than the corresponding diabody. For example, in Example 7 and Figure 6 of the present application, Applicants have shown that an sc(Fv)2 exhibited a significantly greater half-life than its corresponding diabody. These results certainly could not have been predicted based on Kortt's teachings. Consistent with the holding in *Adams*, Applicants respectfully submit that Applicants' claimed invention is not obvious over Ozaki and Kortt.

Accordingly, Applicants respectfully request that the rejection of claims 1-7 and 22-24 as being obvious over Ozaki in view of Kortt be reconsidered and withdrawn.

CONCLUSION

Applicants respectfully submit that all pending claims are in condition for allowance, and therefore request the timely issuance of a Notice of Allowability.

If the Examiner has any questions regarding this application, she is invited to call the undersigned at the telephone number given below.

Other than excess claims fees, no additional fees are believed to be due with this filing. Please apply the excess claims fees and any other fees that might be due to Deposit Account No. 06-1050, referencing Attorney Docket No. 14875-0166US1.

Respectfully submitted,

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